

Surgeon General

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Director, National Cancer Institute

Congressman Mahon's Letter of September 19 Concerning Leukemia

Congressman Mahon's letter poses several questions which I have paraphrased to assure that fairly complete answers can be made.

1. What is being done in research on leukemia?

Research on leukemia is very extensive and intensive. In proportion to the number of deaths, far more effort and money is devoted to research on leukemia and related lymphomatous forms of malignancy than on almost any other single type of malignant disease. One of the chief reasons for this is that this type of cancer lends itself more readily to study in man and in experimental animals, and it may be illustrative of other types of malignant disease. The types of investigations in progress are directed toward discovery of cause(s) (etiology), prevention, diagnosis, and palliative and curative treatment.

The research on causes concerns itself primarily with the possibility that viruses, ionizing radiation, hormones, genetic factors, certain types of chemicals, and other factors or agents may be the exciting or contributing causes of leukemia.

In animals, each one of the specific factors or agents mentioned has been shown to influence the occurrence of leukemia and lymphomas but, usually, it appears that more than one factor is involved. A great deal of work is in progress on viruses and on radiation as causes of leukemia in animals and on ways to prevent their effects. Much remains to be learned. There seems to be no question that viruses are causally related to leukemia and leukemia-like malignant diseases in chickens and mice. Also, there seems to be little doubt that radiation dosage, but still low enough to avoid early death, can induce leukemia in animals and man. The many factors that influence the final induction of leukemia and of other cancers are not fully understood and are being studied.

In man, the effect of high but non-lethal radiation exposure of bone marrow and lymphoid tissue is known to induce leukemia. The reaction of individuals is, however, quite variable. At low levels of radiation, also,

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the variability becomes great and the role of radiation in the induction of leukemia becomes less impressive (see Science for September 28, 1958, pp.693-699). The information available is derived from accidents and the atomic bomb blasts in Japan. Other information is being restudied and evaluated to learn whether short or long exposures to low levels of radiation will significantly affect the induction of leukemia in man.

Viruses have not been shown to cause leukemia in man despite many efforts. With newer evidence from animal studies and with newer techniques, vigorous investigation along this line is in progress. Most of these studies have to be indirect because of the lack of an experimental animal that will experience the same disease as man and to which man's disease can be transmitted. Analogous experimental animal subjects and other approaches and techniques are being sought. Pending success in this, however, investigators will continue their search with less direct means of identification.

If one can identify the cause(s) of leukemia, or of any form of cancer, it may be possible to prevent the action of the causes or neutralize their effects. Thus, if the cause is certain levels of radiation or certain chemicals in the air or food or water, it should be possible to shield most of us from them or neutralize them. If viruses are responsible for leukemia in man, as it is evident they are for some types of leukemia in mice and chickens, vaccines or anti-sera might be protective and preventive. Many investigators hopefully look for such possibilities.

Considerable effort and funds are devoted to studies of blood and of leukemia cells and their normal counterparts in the hope that sufficiently striking differences can be found (a) to improve the ease and reliability of diagnosis at an early stage in the disease, and (b) to provide a basis for treatment with agents which will destroy the leukemic cells and their source of origin without serious damage to the patient's normal cells. Studies of this type are directed chiefly at the biochemical characteristics of cells. Progress is being made in learning more about cells and the blood, but the differences between normal and leukemic patients are not distinctive enough yet to provide the clues that are being sought. Some of this knowledge has been the basis for developing and trying new chemicals for treatment of leukemia.

In the area of therapy of leukemia, there is the greatest emphasis. Through the Cancer Chemotherapy National Service Center and the Cancer Chemotherapy National Committee increased efforts have been in progress to mobilize chemists, biologists, biochemists, pharmacologists, microbiologists, and clinical investigators in a major program to discover better chemotherapeutic agents and better ways of using those available

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in the treatment of cancer. A large number of investigative groups have joined in cooperative studies to assess the agents currently available and to prepare for the trial of new compounds that are hoped-for from the program of drug development. Many of these clinical groups are primarily studying leukemia. One of them has participating hospitals in Texas, Louisiana and Arkansas. In addition, the cooperation of the pharmaceutical industry has been obtained and many industrial research groups are actively working toward discovery of new anti-cancer agents.

Although much has been learned from these studies and those that preceded, no cure for leukemia has been discovered. Nevertheless, it is encouraging to realize that the survival time for children with acute leukemia has been more than doubled, and that for some types of leukemia in adults there appears some improvement. The mustard gas derivatives, anti-folic acid compounds, steroids, radioactive isotopes, external radiation, and other forms of therapy that have been developed in the past fifteen years have added significantly to the life span, the comfort and the hope of the leukemic patient. These developments and the intensive efforts now in progress offer encouragement to hope for still more and better results in the near future.

2. Is the financing of research on leukemia by public and private sources adequate?

I feel obliged to say that to the best of my knowledge and according to the advice I receive, the greatest shortage in the fight against cancer is that of ideas and of adequately trained scientists. The Congress has for the past two years provided sums adequate to support all of the cancer research project grants recommended by the National Advisory Cancer Council. As nearly as we can predict now, it seems that the appropriation for research grants for the current fiscal year, increased by \$6,755,000 over last year, will probably be adequate to support all grants that will be recommended by the Council. We hope that the increases in funds voted by the Congress for cancer research fellowships (\$400,000) and cancer research training grants (\$1,355,000) will provide for the training in research of all properly qualified candidates. It is to the men now in training or who have recently completed training in research that we look for new ideas and new approaches to the problem of cancer as well as further intensive exploration of the older leads that are proving fruitful.



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3. Can anything more be done to prevent or cure the disease? Specifically, is there anything more that the Public Health Service can do or that the Congress can do to cope with this problem?

In view of the funds currently provided by the Congress and of the intensive efforts by the Public Health Service through the National Cancer Institute and through the cancer control programs of the Bureau of State Services, I cannot honestly say that I believe there is anything more that the Public Health Service or the Congress can do than to follow with eagerness and sympathy every promising lead that develops. It is to be expected that as new men are trained and become independent investigators, and as research opens new leads, there will be increased needs and increased opportunities to aid research. Until the tide of cancer is turned, it is likely that a regular and gradual annual increment of support will be needed, but until there comes the much hoped for breakthrough, I do not anticipate a need for sharply increased funds. I should add, however, that we welcome every idea of how to do a better job. In reviewing these, the members of the National Advisory Cancer Council have kept their eyes and minds open but have been equally alert to recommend support for ideas that are clearly reasoned and for work by investigators who have presented a sound plan for research.

Perhaps I should point out that in addition to the funds provided by the Congress for allocation through the National Cancer Institute on recommendation by the National Advisory Cancer Council, there are available funds from several other semi-private and private sources for support of research on cancer, including leukemia. The Public Health Service, through the National Cancer Institute, keeps in close liaison with such agencies.

4. Is there any evidence that leukemia occurs more frequently in geographical areas associated with higher altitude, more sunshine and less humidity and rain, and more exposure to atmospheric radiation? If so, are these possibly causal factors in the initiation and development of leukemia?

Environmental factors that might cause or contribute to the induction of leukemia have been sought. As indicated above under the answer to question #1, high levels of radiation are known to induce leukemia in man. There is considerable uncertainty, however, whether lower levels have a proportionate effect. Much attention is being given to this, as you know. We have been reviewing the mortality rates for different types of cancer in different parts

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of the country and of the world for special cases that would give us a lead to search for some specific cause. Although there is a slightly higher mortality from leukemia in the southwestern part of Texas as compared to the rest of the state, the difference would seem of doubtful significance because the figures are so small. As far as altitude and atmospheric radiation are concerned, Denver might seem comparable. Here the figures are not significantly different from other lower parts of the country. While sunlight is believed to play a part in the higher frequency of skin cancer, I am told that the vital statistics do not suggest a similar relation to leukemia.

The figures on which to base an answer to the foregoing question are not as extensive as one might wish. Since Miss Eleanor Macdonald, biostatistician at the University of Texas M. D. Anderson Hospital and Tumor Institute, has been making a special effort to obtain reliable data on the relative frequency, morbidity and mortality for different forms of cancer for all of the counties of Texas, it may be that she has some information that we are not yet aware of. I am asking her if she will comment directly to you on this subject.

5. How can non-profit research organizations secure Federal funds for the procurement of needed equipment, etc., within the framework of existing law?

Support for research in any area pertinent to health problems may be sought from the National Institutes of Health by any organization or individual, according to the act of Congress. Applications are received three times a year, before July 1, November 1 and March 1 for review by National Advisory Councils at corresponding meetings in October-November, February-March, and June. Such applications may request aid for almost any type of research need. Requests for research facilities construction require special forms and are reviewed by a special Council. Research grants and research training grants are reviewed by Council associated with one of the Institutes of the National Institutes of Health, as for example, the National Advisory Cancer Council for applications related to cancer grants. Applications may request funds for research personnel, equipment, consumable supplies, travel, indirect costs, and any other legitimate cost of the conduct of research. These requests are first reviewed for technical qualities by special committees of experts drawn from the research laboratories of the country. These Study Sections, as we call them, are made up of research leaders in various fields such as cancer chemotherapy, biochemistry, radiation, general medicine, hematology, pathology, endocrinology, etc. Then the final recommendation is made by a National Advisory Council, such

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as the National Advisory Cancer Council. These Council are made up of scientists, physicians, and laymen who are particularly interested in and qualified in the area for which they are responsible. According to the law, the Surgeon General may award a grant only if it has been recommended by the National Advisory Cancer Council. He may veto such a favorable recommendation, but he may not award a grant without a favorable recommendation.

To seek a grant under the terms described above, the applicant should ask for application forms from the Division of Research Grants of the National Institutes of Health and return his completed application there. It will be reviewed by the best qualified persons we can find to advise me. It is important that the application carefully present a clear picture of what the investigator wishes to do, including a sound and carefully designed research plan. Too often the proposals are not sufficiently well planned, or the investigators show insufficient evidence they are qualified to carry them out. In such cases, the National Advisory Councils decline to recommend support for the proposals. The rejected applicant is always entitled to reapply for either the same or another project.

Since the Wadley Research Institute of Baylor University Hospital at Dallas has been mentioned, it may be of interest to know that the National Cancer Institute has supported the work of Dr. M. D. Frager there. Also, after an application from the Director, Dr. Joseph Hill, was not recommended, several members of the National Advisory Cancer Council, two members of the Cancer Chemotherapy Study Section, and two staff members visited the Institute two years ago. Suggestions were made as to how a more adequate proposal might be developed and reapplication was invited. No further application has been received. I am sure the National Advisory Cancer Council would welcome the chance to review a well planned research proposal that they could recommend with enthusiasm.

We shall be pleased to furnish additional information if Congressman Mahon desires on the above or other details of the problem of leukemia.

J. R. Heller, M. D.

Attachment